Simulation Modeling of Gastrointestinal Absorption

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INTRODUCTION

Mathematical dosimetry models incorporate mechanistic determinants of chemical absorption, distribution and elimination in a living organism to describe relationships between exposure concentration and some target tissue dose needed for human health risk assessment. These mechanistically-based models may be used predictively to examine interspecies differences as well as differences between adults and children.

One component of such models is the description of how the substance crosses a barrier (the lining of the respiratory tract, gastrointestinal tract, or the surface of the skin) and enters the internal environment of the body. The gastrointestinal tract is actually a single tube with varying cross-section. Material is transported longitudinally through the tube and is removed from the walls of the tube. On the simplest level, it can be assumed that substances exit through the cell layer lining the GI tract by diffusion which can be modeled by Fick's first law as a first-order absorptive process. However, this is absolutely true only for small compounds but may be approximately true for larger molecules or for molecules that undergo active transport from the GI tract into the bloodstream.

The transit time of material through the GI tract can change depending upon the composition of the meal ingested, complicating the estimate of absorption. These are the types of issues which must be addressed in a predictive GI uptake model. This poster examines the use of a compartmental uptake model to predict the absorption of two compounds: Trichloroethylene (TCE), a highly permeable compound and insulin, a compound with low permeability.

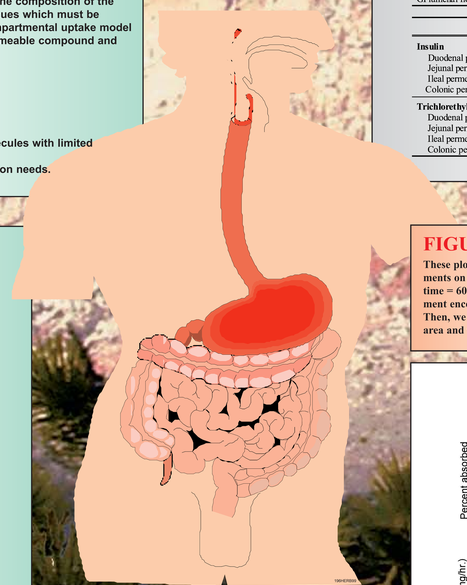
GOALS

To examine the use of compartmental models approximating the GI tract.
To delineate the types of models needed to describe the uptake of larger molecules with limited permability and smaller more permeable molecules.
To begin to examine the sensitivity of model parameters to focus data collection needs.

BACKGROUND

Gastrointestinal Components

- Mouth
- Esophagus
- Stomach
  - Acid pH (<2)
  - Storage, mixing function
  - Fight infection
  - Partial protein, carbohydrate digestion, but little absorption
- Small Intestine (Duodenum, Jejunum, Ileum)
  - Neutral to basic pH
  - Digestion and absorption of fats, proteins, carbohydrates
  - Water absorption, active absorption of ions
  - Likely the sight of absorption for most environmental chemicals
- Large Intestine (cecum, Colon, Rectum)
  - "Tight junctions", active ion absorption
  - Water absorption



Dosimetry Model Types

Distributed Parameter (Tube) Models
- Incorporate detailed anatomic information and true geometry.
- Concentration depends on time and spatial position.
- Must solve fairly complicated partial differential equations

Lumped Parameter (Compartmental) Models
- Sometimes called "compartmental models".
- Divide the body into regions that can be simulated as well-mixed compartments.
- Can incorporate some physiological information.
- Described by ordinary differential equations, simpler to solve.

PARAMETERS

Physiological parameters

Parameter	Base Value	Source
Duodenum		
Volume	123 ml	Guyton (1991)
Surface area	196*600=117600 cm^2	Calculated
Jejunem		
Volume	1227 ml	Guyton (1991)
Surface area	1963*600 = 1,177,800 cm^2	Calculated
Ileum		
Volume	1718 ml	Guyton (1991)
Surface area	2749*300 = 824,700 cm^2	Calculated
Colon		
Volume	4524 ml	Guyton (1991)
Surface area	3018 cm^2	Calculated
GI lumenal flow rate	120 ml/hr.	Dressman *et al.* (1984)

Chemical-specific parameters

Insulin		
Duodenal permeability	4.08 x 10^{-5} cm/hr	Sinko *et al.* (1993)
Jejunal permeability	4.08 x 10^{-5} cm/hr	Sinko *et al.* (1993)
Ileal permeability	1.5 x 10^{-4} cm/hr	Sinko *et al.* (1993)
Colonic permeability	0.0	estimated
Trichloroethylene (TCE)		
Duodenal permeability	1.05 x 10^{-3} cm/hr	Clewell *et al.* (1997)
Jejunal permeability	1.05 x 10^{-3} cm/hr	Clewell *et al.* (1997)
Ileal permeability	1.05 x 10^{-3} cm/hr	Clewell *et al.* (1997)
Colonic permeability	1.05 x 10^{-3} cm/hr	Clewell *et al.* (1997)

FIGURE 1.

We designed a four-compartment model of the gastrointestinal tract using MATLAB SIMULINK Software (Mathworks; Nattick, MA). Compartmental parameters are listed in the table at left. The stomach was not independently modeled, but stomach emptying via the pyloric sphincter was modeled as a periodic pulse input into the duodenum.

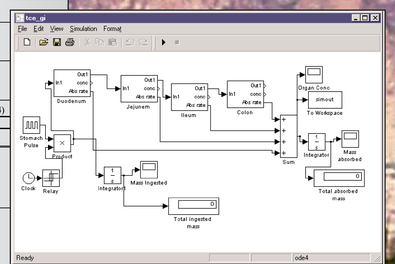
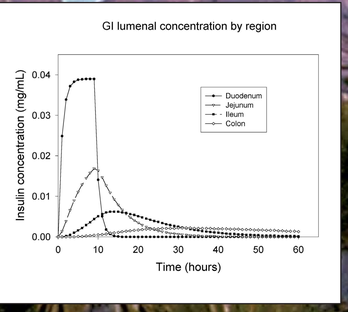


FIGURE 2.

The concentration in each intestinal region from a simulation run for 60 hours after a single dose of insulin to the stomach. It is assumed that the dose is instantly 100% dissolved and available in the stomach but that it takes several hours to empty the stomach contents into the intestine.



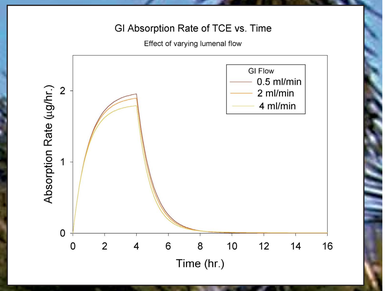


FIGURE 6.

For highly permeable compounds like TCE, changes in transit time have little effect on absorption rate. Here, the absorption of TCE is examined at 3 different lumenal flow rates: 0.5 ml/min (30 ml/hr), 2 ml/min (120 ml/hr), and 4 ml/min (240 ml/hr). The dose of TCE was 8 mg which is equivalent to drinking just over 1.5 L of water per day with a water concentration of TCE at the MCL of 5 mg/L. The entire dose is assumed to traverse the stomach in 4 hours. The total mass absorbed ranged from 91 - 97% of the administered dose.

FIGURE 3.

These plots indicate the effect of increasing the number of compartments on absorption in a GI model. Insulin dose = 45 mg. Simulation time = 60 hours. We reduced the original model to a single compartment encompassing the entire volume and surface area of the GI tract. Then, we increased the number of compartments such that the surface area and volume were equally distributed.

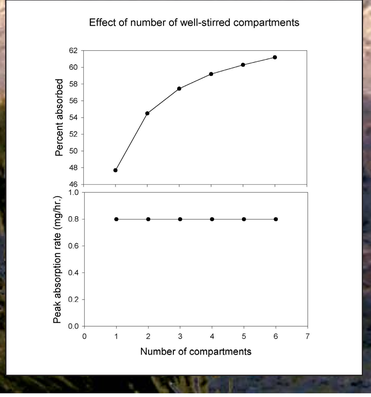


FIGURE 4.

This plot shows the effect of the flow rate of ingested material through the GI tract on total absorption of insulin after a 45 mg ingested dose. The model was the four-compartment model (Figure 1). The vertical line represents a "normal" GI flow rate, although the whole range is physiologically realistic. Experimental data indicates that on average a 50 mg dose of insulin is 55% absorbed. (This model does not take into account the extensive metabolism of the compound at the intestinal wall.)

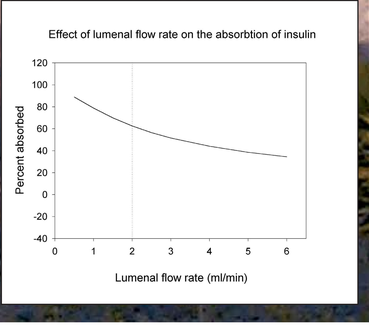
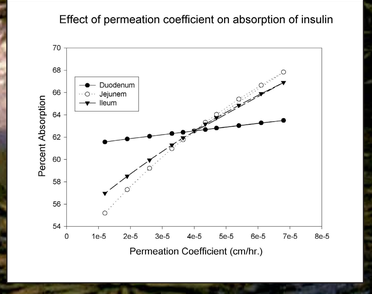


FIGURE 5.

This plot depicts the sensitivity of the model output to intestinal permeability parameters in each compartment. This provides an indication of how likely uncertainty in the permeability will create large errors in the absorption estimate. This plot indicates that there is relatively little sensitivity for the total absorbed. However, this doesn't provide any information about absorption rate.



CONCLUSIONS

The overall absorption of insulin may be adequately simulated with a series of 4 to 6 well-stirred compartments.

If permeability is independent of flow, then increasing GI flow rate reduces the total amount of insulin that is absorbed.

For highly permeable compounds such as TCE, transit time does not have a large affect on absorption rate or total amount of material absorbed, suggesting that models may be collapsed to fewer compartments.

Future modeling work must include changes in solubility and ionization state as a function of pH.

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